REMARKS

It is requested that the request for continued examination be granted. This preliminary amendment is a proper submission pursuant to 37 C.F.R. 1.114(c). It is further requested that this preliminary amendment be entered.

Claims 1, 54-58, 60, 63, 65 and 67-75 are pending in this application. Claims 2-53, 59, 61, 62, 64 and 66 have been canceled without prejudice or disclaimer. Claims 1, 58, 60, 67 and 70-73 have been amended.

Rejection Under 35 U.S.C. § 101

Claims 1 and 58 stand rejected under 35 U.S.C. § 101 "because the claimed invention is directed to non-statutory subject matter." The Examiner maintains that the "obtaining and testing steps [set forth in the claims] are computational in nature rather than laboratory chemistry ...." Claim 1 has been amended to change "obtaining" in Step (B) to --selecting--. The Examiner directed Applicants' attention to claim 54 which is dependent on claim 1 and which is directed to testing a compound *in vitro*. Claim 1 has also been amended to recite testing the compound selected in Step (B) *in vivo* or *in vitro*. Support for the amendments can be found at page 8, lines 3-9 of the specification. It is believed that by these amendments, the rejection of claims 1 and 58 is overcome. Accordingly, it is respectfully requested that the rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph Written Description Requirement

Claims 1 and 54-75 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Claims 59, 61, 62, 64 and 66 have been

canceled, thereby rendering this rejection moot as to these claims. According to the Examiner, the specification as filed does not provide for the "broader concept of modulating binding of natural ligands." The Examiner further made a finding that the specification does not support the concept modulating "signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4" and requiring the testing of the compound for its ability to modulate the signal transduction. As we understand the rejection, the Examiner finds that the specification does not support the broader concept of modulation which embraces activation and agonists. In order to obviate this rejection, independent claims 1 and 73 have been amended to replace the term "natural ligand" with a list of EGF receptor ligands. These ligands were well known at the priority date of this application and are recited in the specification on page 1, lines 9-12 and in the references cited throughout the specification. In addition, independent claims 1 and 73 have been amended to limit the claims to a method of screening using the co-ordinates of the EGF receptor provided in Figure 6 and to delete all reference to ErbB2, ErbB3 and ErbB4 receptors from the claims. Also, the following passages in the specification, when read together, provide clear support for the concept of screening for agonists of the EGF receptor:

> Accordingly, in a first aspect the present invention provides a method of designing a compound which binds to a molecule of the EGF receptor family and modulates an activity mediated by the molecule, which method comprises the step of assessing the stereochemical complementarity between the compound and a topographic region of the molecule, wherein the molecule is characterised by .... [Page 4, lines 10-15.]
>
> * * *
>
> In one embodiment of the first aspect, the compound has the ability to increase an activity mediated by the molecule of the EGF receptor family. [Page 6, lines 30-31.]
>
> * * *

> In a further preferred embodiment of the second aspect, the method is used to identify potential compounds which have the ability to increase an activity mediated by the receptor molecule. [Page 7, lines 32-34.]
>
> * * *
>
> In a fifth aspect, the present invention provides a pharmaceutical composition for preventing or treating a disease which would benefit from increased signalling by a molecule of the EGF receptor family, which comprises a compound according to the third or fourth aspects of the present invention and a pharmaceutically acceptable carrier or diluent. [Page 9, lines 29-33.]
>
> * * *
>
> In a seventh aspect the present invention provides a method of preventing or treating a disease which would benefit from increased signalling by a molecule of the EGF receptor family which method comprises administering to a subject in need thereof a compound according to the third or fourth aspects of the present invention. Preferably, the disease is selected from wound healing and gastric ulcers. [Page 10, lines 3-8.]
>
> * * *
>
> Binding affinity and inhibitor potency may be measured for candidate inhibitors using biosensor technology. [Page 16, lines 6-7.]
>
> * * *
>
> ... The second potential mode of action is for the molecule to bind to a site on the EGF receptor which is not necessarily a ligand binding site. Such a molecule may be physically large enough to hinder physical access of a second receptor to the receptor which binds the molecule in question. This would hinder dimerisation and subsequent activation of the receptor. If the molecule is sufficiently "sticky", it may attract a second EGF receptor and induce dimerisation, thereby acting as an agonist rather than an antagonist. [Page 29, lines 19-26.]

The specification also provides adequate methods by which compounds identified by the screening method of the invention can be assessed for agonists or antagonist activity using *in vitro* or *in vivo* assays of hormone function (see, for example, page 15, line 28 to page 16, line 28). A person of skill in the art would immediately understand that the binding affinity assays or cell based assays described in this section of the specification could be readily used to identify antagonists or agonists of the EGF receptor.

The Examiner did not find written descriptive support for claim 57. The claim is dependent on claim 1 and requires in step (C)(ii) the testing of the compound for its ability to modulate the EGF receptor mediated cell proliferation. The claim is supported in the specification at page 16, lines 16-19, which discloses that "[o]nce [the] candidate compounds have been identified, their ability to antagonize signal transduction via the EGF-R can be assessed using a number of routine *in vitro* cellular assays such as inhibition of EGF-mediated cell proliferation." The claim is also supported in the specification at page 15, line 28 to page 16, line 28 wherein there is a discussion is directed to testing compounds, e.g., EGF receptor antagonists for there ability to modulate receptor activating using *in vitro* cellular assays. Accordingly, claim 57 is supported by the specification of the present application.

In view of the above, it is respectfully requested that the rejection of claims 1, 54-58, 60, 63, 65 and 67-75 under the written description requirement of 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph
Enablement Requirement

The Examiner held that if the rejections over the written description requirement were overcome, the claims would continue to be rejected for lack of enablement because (a) the "specification does not exemplify modelling of any compound and a molecule as defined by claim 1(A)(i)-(iii)," (b) the "specification does not disclose any compounds meeting the structural and functional limitations required by the claims" and (c) "the specification does not clearly specify what is required to be performed in assessing "sterochemical complementarity."

The test for enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation. *United States V. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); *In re Stephens*, 529 F.2d 1343, 1345, 188 USPQ 659, 661 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed. Cir. 1984). It is the function of the specification, not the claims, to set forth the practical limits of operation of an invention. *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977).

Examples exemplifying specific compounds or molecules for claimed step(A)(i)-(iii) of claim 1 are not required to support enablement. The specification, as a whole, must be considered to determine if the invention as disclosed is enabled. The invention is directed to a method of identifying a compound that possesses stereochemical complementarity with the molecule as well as possessing the ability to modulate a molecule of the EGF receptor family. The Examiner has not presented any evidence to show that this concept is not known in the art and would require undue experimentation by a person skilled in the art to practice the claimed invention. However, in order to advance prosecution, independent claims 1 and 73 have been amended to delete step (A)(iii) and to limit the claims to a method of screening using the co-ordinates of the EGF receptor provided in Figure 6, i.e. ErbB2, ErbB3 and ErbB4 have been deleted from these claims.

The invention is based on determining the three dimensional structure of a EGF receptor and using the structure as a template (see page 16, line 29 to page 17, line 29 of the specification). The modelling for the EGF receptor is described in detail from page 17, line 31 to page 22, line 35 of the specification. The structure of the EGF template is described in detail at page 23, line 1 to page 24, line 21 of the specification. As described at page 29, lines 14 to 26 of the specification, in one mode if the compound being tested has sterochemical complementarity with the EGF receptor, the compound molecule will compete for binding sites with one of the EGF receptor's natural ligands, i.e,, the molecule will prevent the receptor dimerisation that is required for activation of the EGF receptor. In such an event, the molecule will be acting as an antagonist. On the other hand, the binding of the molecule may act as an agonist. In another mode, the compound molecule may bind to a site on the EGF receptor which is not necessarily a ligand binding site. This too could hinder dimerisation and subsequent activation of the receptor. Thus, the compound molecule would be acting as an antagonist.

In view of these teachings from Applicants' disclosure, the fact that no specific compounds are disclosed is not fatal for enablement. A person having ordinary skill in the art would have known from reading the specification that binding of part of the EGF receptor is required in order to determine the mode of the compound molecule, i.e., whether it is an antagonist or an agonist. There is sufficient enabling disclosure in the specification that would enable a person having ordinary skill in the art to practice the invention without undue experimentation. Taking the disclosure of the specification as a whole, an example of a method using a specific compound is not necessary for practicing the invention and for enablement.

The Examiner made a finding that the claims do not recite any scoring function or cut-off value to discriminate high ranking compounds from low ranking compounds. It is not necessary to provide these cut-off values, particularly in view of the requirement of a selection being made. The concept of "selecting" relates to a choice being made with respect to the best or most suitable compounds in terms of stereochemical complementarity to the molecule of present interest.

The Examiner made a further finding that there is no guidance in the specification as how to select "one or more subsets of said amino acids related to the coordinates shown in Figure 6 by whole body translations and/or rotations". First, Applicants wish to clarify the meaning of "whole body translations and/or rotations". As the Examiner is aware, the coordinates listed in Figure 6 describe the three-dimensional structure of the EGFR ectodomain (amino acids 1-621) in a specific orientation. All computer graphics programs used to study the three-dimensional structures of compounds, e.g. proteins, permit the operator to view the three-dimensional structure from any viewpoint by rotating it (whole body rotations) or moving it across the computer screen (whole body translations). In some programs the operator simply clicks on the graphic on the computer screen and moves it about using the mouse. In more sophisticated programs there are separate interfaces on the computer screen for rotation, translation and zoom. Whole body rotation and translation can be applied to the whole molecule or to selected (defined) subsets of amino acids, e.g. those involved in a potential binding pocket. Selected subsets can be considered as equivalent to 'zooming in' for a closer inspection of the details of the interaction between the selected region of the protein and the docked chemical compound.

Thus, the phrase "whole body translations and/or rotations" would be readily understood by a person having ordinary skill in the art.

The Examiner states that the specification provides no guidance on which subsets of amino acids to choose. A person having ordinary skill in the art would have understood, however, that the "subsets of amino acids" in this phrase corresponds to a potential binding pocket or binding site on the receptor molecule. Please note our arguments set forth on pages 7 and 8 of our response submitted on July 21, 2003, which makes it clear that processes for selecting binding sites would have been well known to those skilled in the art and that the specification provides adequate guidance on preferred binding sites at, for example, at page 5.

The Examiner made a finding that the specification does not clearly specify what is required to be performed in assessing "stereochemical complementarity". In particular, the Examiner asserts that the specification does not provide a specific definition of "stereochemical complementarity". The Examiner acknowledges that page 5, lines 12 -15 defines stereochemical complementarity in the context of 'lock-and-key' visualisation, but finds the additional references to "matching intra-site coordinates lining the groove of the particular receptor site" and the optimal "fit" to be confusing. The terms "stereochemical complementarity", "matching intra-site surface coordinates" and "optimizing, geometrically or chemically, the fit" are all synonymous terms and are commonly used in the art. The phrase 'stereochemical complementarity' was already well known in the art before the priority date of the present application. For example, a search of the PubMed database using the term "stereochemical complementarity" yielded 31

references. See the list of references attached to the response to the final rejection submitted on February 23, 2004, as Exhibit A. Some examples of these references are set out below:

1. Bransome, E.D. et al.; "Apparent stereochemical complementarity of estrogens and helical cavities between DNA base pairs: implications for the mechanism of action of steroids," *J. Theor. Biol.* 1985 Jan 7; **112**(1):97-108.

2. Hendry, L.B.; "Drug design with a new type of molecular modeling based on stereochemical complementarity to gene structure," *J. Clin. Pharmacol.* 1993 Dec; **33**(12):1173-87.

3. Hendry, L.B. et al.; "The stereochemical complementarity of DNA and reproductive steroid hormones correlates with biological activity," *J. Steroid Biochem.* 1986; **24**:843-852.

4. Hendry, L.B and Mahesh V.B.; "Stereochemical complementarity of progesterone, RU486 and cavities between base pairs in partially unwound double stranded DNA assessed by computer modelling and energy calculations, " *J. Steroid Biochem. Mol. Biol.* 1992; **41**:647-651.

We also note that the terms "stereochemical fit" and "shape complementarity" are recited in the claims in U.S. Patent Nos. 4,461,619 and 6,184,241. Copies of the patents were attached to the response to the final rejection submitted on February 23, 2004, as Exhibits B and C, respectively. For example, claim 1 of U.S. Patent No. 4,461,619 defines a method for determining the biological activity of a molecule which includes comparing the stereochemical properties of the molecule with respect to cavities in a nucleic acid complex to determine a

"complementary fit", with a fit indicating the biological activity. Further, claim 1 of U.S. Patent No. 6,184,241 defines an aspartic protease/inhibitor complex wherein a portion of the complex has a "shape complementarity" with at least a portion of the substrate binding site of the aspartic protease. A person skilled in the art would have understood that the concepts of "stereochemical fit" and "shape complementarity" are synonymous with "stereochemical complementarity."

The Examiner asserts that the specification does not clearly imply what is required to be performed in assessing stereochemical complementarity. The Applicants submit that this is covered by reference to the docking programs as set forth on pages 13-14 of the specification. These programs take each chemical compound and calculate the strength of its interaction with the selected binding site on the EGFR by calculating the H-bonds, the geometric shape complementarity, the hydrophobic interactions, the Van der Waals forces and the salt bridges. All of these parameters contribute to the strength of the interaction. Each compound is placed in a large number of orientations and the calculated strengths of these parameters are recorded for each orientation. A person of ordinary skill in the art would clearly understand what is required to be performed in assessing stereochemical complementarity in light of the references provided in the specification.

The Examiner contends that the claims do not require finding a binding pocket, using a known binding pocket or using a docking program. Finding a suitable binding site is inherent in the claim language. The claims require assessing the complementarity between the compound and the receptor molecule. The original claim language referred to assessing the stereochemical complementarity between the compound and a "topographic region" of the molecule. It is

Applicants' position that the "topographic region" referred to a potential binding site on the receptor molecule. At the interview with the Examiner last year on June 24, 2003, the Examiner suggested simply removing the term "topographic region" on the ground that the phrase "assessing the stereochemical complementarity between the compound and molecule" was clearer. We adopted the Examiner's suggestion and amended the claim accordingly. The phrase "one or more subsets or amino acids related to the coordinates shown in Figure 6 by whole body translations and/or rotations" in claimed step (A)(ii) of claim 1 clearly encompasses the concept of identifying binding pockets. In particular, a person of ordinary skill in the art would have understood that the selection of subsets of amino acids is equivalent to selecting a binding pocket for modeling purposes. The specification at pages 4 and 5 provides adequate guidance for selecting suitable "topographic regions" or binding pockets. In particular, on page 6, lines 1-8 of the specification states that

> ...the interaction of the compound causes the L1 and S1 domains to move away from each other. In a further preferred embodiment the compound interacts with the hinge region between the S1 domain and the L2 domain causing an alteration in the positions of these domains relative to each other. In a further preferred embodiment the compound interacts with the β sheet of the L1 domain causing an alteration in the position if the L1 domain relative to the position of the S1 domain or L2 domain.

The patent application goes even further by specifying two sites on the lower β-sheet of the L1 and L2 domains as suitable targets for screening. See, for example, the specification at page 6, lines 9-14. As we pointed out in our last response, Applicants submit that a person skilled in the art working in the field of *in silico* screening would be able to identify candidate binding pockets in any given 3D structure. In the present case, however, the patent application actually identifies

specific "topographic regions" which represent preferred "binding pockets" within the EGFR structure. These binding pockets can be used in screening methods to identify potential ligands and are described as follows:

(i) The fragment which includes residues 1-475 of the receptor, comprises the L1, S1 and L2 domains of the ectodomain of the EGF receptor. At the center of the structure is a cavity, bounded by all three domains, of sufficient size to accommodate a ligand molecule (see the specification at page 5, lines 5-7).

(ii) The fragment, which includes residues 313-621 of the receptor, comprises the L2 and S2 domains, which are positioned such that they form a "corner" structure. It is envisaged that this corner structure provides a further binding site for ligands of EGF receptor family members (see the specification at page 5, lines 8-11).

Accordingly, the patent application not only identifies the binding pockets within the EGFR structure, but suggests preferred regions within these binding pockets to use in screening for ligands. Armed with the atomic coordinates of the EGF receptor provided in the patent application and the information regarding preferred regions within specified binding pockets, it would have been a matter of routine for a person skilled in the area of *in silico* screening to utilize any one of the well known docking programs to screen for potential ligands.

Accordingly, for all of the foregoing reasons, it is respectfully requested that the rejection of the claims as lacking enablement under 35 U.S.C § 112, first paragraph, be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 54-75 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 59, 61, 62, 64 and 66 have been canceled, thereby rendering this rejection moot as to these claims. The Examiner's Advisory Action stated that this rejection under 35 U.S.C. § 112 is being maintained because the specification does not provide definitions for "natural ligand" and "equivalent three-dimensional structure". These terms have been deleted from the claims as proposed to be amended. Also, the Examiner found the phrase "signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4" to be indefinite. Independent claims 1 and 73 have been amended to delete "ErbB2, ErbB3 or ErbB4." Also the term "via" has been changed to -- by binding to-- to clarify that the compound selected modulates signal transduction by binding to the EGF receptor.

The Examiner contends that "it is not known what the increase, decrease or inhibition" is in comparison to or when this step occurs within the method of claim 1. In our view this comment lacks merit. Step (C) of claim 1 requires testing the compound for its ability to modulate signal transduction by binding to the EGF receptor. A person of ordinary skill in the art would readily appreciate that the modulation, i.e. increase, decrease, or inhibition, would be relative to a control in which the compound is not present. The language of the claim would have been understood by a person having ordinary skill in the art to mean that the increase, decrease or inhibition would occur during step (C) of claim 1, i.e. during the *in vitro* or *in vivo* testing.

The Examiner finds that the phrases "substantially as shown" and "form an equivalent 3-dimensional structure" are indefinite and unclear. In order to obviate the objection to the phrase "substantially as shown", the phrase "substantially" has been deleted from the claims. As for the objection to the phrase "form an equivalent 3-dimensional structure," this phrase has been deleted from the claims.

The Examiner contends that there is no antecedent basis in claim 1 for the phrase "the molecule". The first appearing "the molecule" in claim 1 has been amended to recite --a molecule--. It is believed that by this amendment, the rejection is overcome.

The Examiner objects to claims 62 and 67 on the ground that the step of modifying the compound is confusing. In order to obviate this rejection, claim 62 has been canceled and claim 67 has been amended to recite that, *inter alia*, the step of modifying the compound selected in step (B) or step (D) enhances the modified compound to bind to a lower face containing the second β-sheet of the L1 and/or L2 domains when compared to the unmodified compound.

Finally, the Examiner has objected to claim 73 as being unclear because it is not clear whether the K_d or K_I is "a predicted, calculated or experimentally determined value." Claim 73 has been amended to clarify this portion of the claim and to specify that the K_d and K_I are experimentally determined.

For all of the foregoing reasons, the rejections should be overcome by the amendments to the claims. It is respectfully requested that the rejection of claims 1, 54-58, 60, 63, 65 and 67-75 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

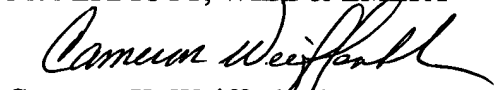
Conclusion

It is submitted that the claims 1, 54-58, 60, 63, 65 and 67-75 are patentable and that favorable reconsideration of the claims is requested in light of the preceding amendments and remarks. It is requested that the RCE be granted and that this preliminary amendment be entered. Allowance of the claims is courteously solicited.

If there are any outstanding issues that might be resolved by an interview or an Examiner's amendment, the Examiner is requested to call Applicants' attorney at the telephone number shown below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due under 37 C.F.R. § 1.17 and in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,
McDERMOTT, WILL & EMERY



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